A STUDY ON QUALITY, EVALUATION AND RATIONAL USE OF MEDICINE WITH REGULATORY PERSPECTIVES

By

Ahmed Nawaz Khan

SYNOPSIS

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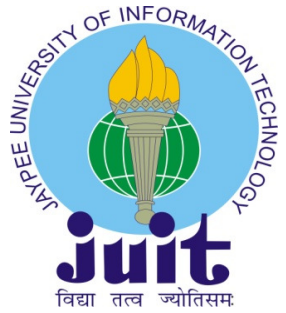
Dr. M. Udayabanu

&

Co-supervision of

Prof. (Dr.) Roop K. Khar



DEPARTMENT OF PHARMACY

JAYPEE UNIVERSITY OF INFORMATION TECHNOLOGY

WAKNAGHAT, SOLAN-173215, INDIA

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Introduction

Patient safety has become one of the most significant factors in the healthcare and concerns equally to all the stakeholders. In terms of pharmaceuticals, ensuring patient safety requires good quality of medicines, less side effects or adverse effects and rational use of medicines[1]. Ensuring public care is a national priority, thereof Indian regulatory authorities, industries, medical practitioners, pharmacist, nurses and even patient as well has a significant role in creating safety culture across the India. Involvement of people as a well active, concerned and informed consumer may help in making their healthcare experience safer and better. Medicines are the source to treat, cure and mitigate the disease conditions. However, irrational use of medicines in terms of prescribing, dispensing, selling and consumption is a worldwide problem[2]. These situations emerge as challenges for the regulatory authorities. Among them first challenge is the quality of medicines, as over the past two decades; providing safe and quality products has become a major area of drug regulation and scientific analytical investigation. Prevalence of poor quality drug or substandard product encounters a major stringent issue for the global health system[3] and it cannot be ignored. Day by day availability and detection of spurious/falsely-labeled/falsified/counterfeit (SFFC) or not of standard quality (NSQ) medicine in the market deteriorate the public credibility in health system. Consumption of these medicines can be responsible for failure of treatment or even death[4]. However, some of the complicating factor which may affect the quality of the drug products are less or more than the label claim, unwanted excipients, impurity and sometimes no active pharmaceutical ingredient (API)[5]. Considering the expansion of the pharmaceutical industry and the degree of potentially mortal diseases, any amount of substandard or spurious medicines is unacceptable because it rises the morbidity and mortality[6]. Even such medicines are the most possible suspect for the antimicrobial resistance in case of antibiotics and treatment failure[7]. And they also induce loss of confidence in health systems and health workers; economic loss for patients and their families; and business loss to the genuine producers[8]. According to Partnership for Safe Medicines (PSM) organization; India is the largest manufacturer of generic medicines and probably 12-25% of the medicines supplied globally are contaminated, substandard and counterfeit[9]. According to Central Drug Standard Control Organization (CDSCO); estimation of the data during 2003-2008 indicates 6.3-7.5% of the samples were of substandard quality and 0.16-0.35% were encountered as spurious[10]. Moreover, a nongovernmental study in 2008 reported that 12% (N=281) and 5% (N=260) samples from Delhi and Chennai respectively; were found to be of substandard quality[11]. In 2011-2012 across the country; CDSCO reported 3.71% substandard products and 0.06% spurious while in 2013-2014, 3.66% products were reported as substandard and 0.25% spurious[12]. The problem of poor quality is already very serious that steadily growing and is likely to cause much more damage in the near future[13]. Only few published data admit the extent of the problem and its influence on the public health. Thus, surveying the pervasiveness of low quality medications is a fundamental need for ensuring the welfare and benefits for all the associated sections. Recently no study has done so far in India except few CDSCO evaluation studies. Therefore, there is requirement of immediate attention and research towards this public safety issue.

Second important challenge for the regulatory authorities is the evaluation process of these large numbers of products. India has more than 8100 manufacturing units for drug formulations[14] and seven national testing laboratories, while there are 134 approved private testing laboratories[15]. If on an average each manufacturing unit produces 15 products, it means there must be more than 100000 drug products in the market. Quality monitoring of these market products are only done in national testing laboratories and the annual average evaluation capacity of all these laboratories is only 15000 samples[12]. Therefore, a challenge rises for the evaluation of the rest of the products in the market. One way to solve this issue is to increase the number of testing laboratories and other is to use some alternate techniques which are fast and efficient for large number of samples. Evaluation of the drug product are generally done by thin layer

chromatography (TLC), infrared spectroscopy (IR), high performance liquid chromatography (HPLC), mass spectrometry (MS), colorimetric methods, dissolution assay and visual inspection; which are considered as well established and pharmacopoeial recognized techniques[16]. However there are certain complications with most of these pharmacopoeial approaches like the invasive nature of analysis, consumption of organic and inorganic solvents, sample preparation, elution of hazardous waste and time consuming. For these reasons efficient analytical approaches with rapid, reliable and non invasive nature are required primarily for routine drug analysis specifically for large number of samples. Hence to overcome such difficulties; Fourier Transform (FT) near infrared spectroscopy (NIRS) has already been proven as a significant analytical technique not only for pharmaceutical product quality estimation but also for detection of counterfeit or spurious drugs at a very low cost with little or no sample preparation[17]. However, it is not a standalone technique thus require some mathematical calculations. Therefore, development of NIRS model requires chemometric analysis in combination with NIRS that defines the scope of NIRS procedure or model used for the intended purpose[18]. Chemometric like principle component analysis (PCA), partial least square (PLS), principal component regression (PCR), discriminant analysis (DA) and soft independent modeling of class analogy (SIMCA) are some of the widely used methods[17]. However, they require expertise and supervision to avoid unstable calibration model.

Likely poor quality medicines are one of the possible suspect for the treatment failure, irrational use medicines is also responsible for such breakdown. Therefore, third challenge is the irrational use of medicines. Medicines are inappropriately, ineffectively and economical inefficiently used throughout the global healthcare system; specifically in developing countries[19]. "The overuse, underuse or misuse of medicines results in wastage of scarce resources and widespread health hazards"[2]. Poly-pharmacy, unseemly use of antimicrobials, prescribing medicines not in accordance with clinical guidelines, ill-suited self medication and patients' non adherence to the treatment are some of the irrational use of medicines[2]. And this non adherence issue is exceedingly common in medical care[20]. Some of the major cause include poor quality of medicines[21]; cost of medicines, side effects and patient behavior[22]–[24]. Indian government and regulatory authorities have stepped up various program and schemes for the patient care and patient safety. However, there are only limited evidences available on effective interventions in improving adherence in India like fixed dose combinations; recommendation of generic medicines to reduce cost burden on patients and prolonged or sustained release medicines. Moreover these interventions are irrespective of unknown prevalence of non adherence. In India, great emphasis is placed on monitoring the adverse effects under Pharmcovigilance Program of India (PvPI) and less concern is paid on non adherence and this lacking focus on the use of medicines recognizes that a functional planning is a prerequisite to being able to implement some other interventions. Like poor quality drugs[7]; patient non adherence also engender antimicrobial resistance[25] and is a rising concern to medical services suppliers and payers on the grounds that it builds the expense of consideration and results in poor patient care[26]. Ample numbers of patients don't get the utmost advantage of medicinal treatment ending in increase the healthcare cost, poor quality of life and deprived health[27], [28]. In chronic disease report from developed countries suggest 50% adherence only[29], while magnitude of the problem is quite big in developing nations[30]. Today, India does not have much information and evidence on non adherence. Among few reported studies; a study of tuberculosis patients (N=538) showed 16% patients non adherence to the treatment[31] and another study of schizophrenia patients (N=115) showed 41.9% patients non adherence to the treatment[32]. One study on hypertensive patients signified 24.1% (n = 114) adherence. It means non adherence was 75.9%[33]. Adherence relates to following suggestions given by the physician with respect to timing, dose and frequency of administration[34]. More specifically following the instructions of medical practitioner is termed as compliance[34]. These terms can also be used interchangeably. One way to measure the adherence is ask practitioner and patient for their subjective rating of adherence response[30]. Even exploring the quality of large

number of market products is a big challenge thus under such monitoring events we can also monitor the poor quality medicines as the actual quality in terms of therapeutic action and adverse effects can only be observed by the medical practitioners (MP) who prescribe them. Therefore, well informed and practice is of the elemental significance to MP for their professional endeavor. Observations from such study will help in making better policies and interventions to improve the public health. Therefore a holistic attempt must be initiated to work on these issues for protecting and promoting the public health.

To study these issues we worked on the following objectives:

- **Objective 1:** To evaluate quality of amoxicillin trihydrate and diclofenac sodium generic products available in the Indian market

- **Objective 2:** To develop and validate identification and quantification models using near infrared spectroscopy and chemometric analysis for :
  (a) amoxicillin trihydrate capsule; and
  (b) diclofenac sodium tablet

- **Objective 3:** To conduct two cross sectional survey :
  (a) to demonstrate medicine prescribing preference by medical practitioners and their perspective for medicine therapeutic response and adverse effects with respect to quality of medicines; and additionally to demonstrate the patient compliance;
  (b) to demonstrate the prevalence of treatment adherence and compliance by patients; and most imprudent age, gender and monthly income groups of patients with respect to rational use of medicines

Objective 1

To evaluate quality of amoxicillin trihydrate and diclofenac sodium generic products available in the Indian market

In recent years no study has been done overall or for individual drug to explore the situation leaving behind no clear documentation on the current extent of the problem. Hence the purpose of this pilot study was to explore quality in terms of content assay of amoxicillin trihydrate (AMOX) and diclofenac sodium (DICLO) products; and the scope is to create awareness among patients and attention to regulatory bodies to evaluate such products. Most often used medicines like amoxicillin, azithromycin, metformin and diclofenac etc. should be on priority to evaluate. Thus we choose amoxicillin trihydrate capsule and diclofenac sodium tablet products based on their often prescribed pattern[35], [36]. For amoxicillin trihydrate capsule evaluation we used Indian Pharmacopoeia 2010 recommended method[37], while for diclofenac sodium tablet we developed a new HPLC method because the recommended method was Ultra Violet spectroscopy method which is considered as primitive method and not that much accurate for the market product evaluation.

Material and Instrument

Amoxicillin trihydrate and diclofenac sodium reference standard (RS) were directly purchased from Sigma Aldrich. AMOX and DICLO API and excipients for placebo were provided by the Ranbaxy (India) as gift samples. HPLC grade acetonitrile (Lichrosolv), methanol (Lichrosolv) potassium dihydrogen phosphate (LiChropur), potassium hydroxide GR grade, phosphoric acid (EMSURE) and monobasic sodium phosphate GR grade were procured from Merck (India). Polytetrafluoroethylene (PTFE) filter of 0.45 µm and nylon filters of 0.20 µm pore

size from Millipore system (Millipore Inc., USA) were used throughout the evaluation. Water used was purified through a Millipore Milli-Q (Waltham, MA, USA) water system.

A HPLC system (Waters, Milford, MA, USA) equipped with Alliance 2695 separations module and photodiode array detector was used in this study. A reverse phase octadecylsilane bonded C-18 (250mm×46mm, 5µm) column (Waters) was employed throughout the analysis. All samples for evaluation were weighed on high sensitive analytical balance TB-215D (Denver Instrument, Germany). Chromatograms were recorded and processed using Empower Pro Software (Waters).

Method

Generic products collection

A total of 46 AMOX generic products were collected which comprises 43 different capsules and two tablets having 250 mg dose. Among them one capsule product was collected of two batches thus in total 46 products were collected. Similarly, 32 DICLO products were also directly procured without prescription from storefront wholesaler or retailer of open market located in urban and semi-urban areas of Northern India.

Amoxicillin standard and sample preparation

All samples were prepared according to the Indian Pharmacopoeia (IP) 2010 amoxicillin capsule monograph. Ten capsules of each product were used per test sample. Against the mean area of five injection of AMOX RS assay of amoxicillin in test sample was determined on percent label claim of API present in individual capsule. The assay requires to be within 89.5%–110.6% of the label claim as per IP[37], [38]; and equal or more than 84.5% according to the Central Drug Standard Control Organization (CDSCO) guidelines to pass standard quality[39].

Similarly, ten tablets of each product of DICLO were transferred in to 100 mL amber color volumetric flask that was made up to a concentration of about 0.20 mg per mL of DICLO. For calculating the precise assay result for diclofenac; %RSD of two preparations was fixed not to be more than 2. For assay; to pass the pharmacopoeia specification each product must be within 89.3%–110.8% of the label claim[40], [41]. While according to CDSCO, product which fails assay 5% below the pharmacopoeia specification that is below 84.3% were considered to be substandard product or NSQ[39].

Assay method development and validation for diclofenac sodium

A new HPLC method was developed using reference of United State Pharmacopoeia monograph of diclofenac sodium tablet. DICLO-RS was used as a control. A blend of microcrystalline cellulose, talc, croscarmellose sodium, magnesium stearate and colloidal silicon dioxide was prepared and assumed as placebo. In accordance with the Q2(R1) International Conference on Harmonization (ICH) guidelines method was validated with recommended parameters which include specificity, linearity, accuracy, precision and robustness [42]. Validation sample set were quantified against mean peak area of six injections, to pass the system suitability criterion; %RSD was fixed not to be more than 2. Overall %RSD for robustness was fixed not to be less than 2 and peak purity must pass.

Result for amoxicillin trihydrate

System suitability was demonstrated to be appropriate for routine analysis purpose, thus AMOX RS peak was confirmed by match plot at 230 nm. Peak purity was checked with the higher purity threshold than purity angle. In order to compare the quality of AMOX capsules, we identified its presence and calculated the amoxicillin proportion with respect to label claim. Out of 46 products the percentage content of 13 products were not matched with the label claim. As shown in

Fig.1, 13 products were failed to follow the IP specification. And among them six products were failed to follow the recommended limit of CDSCO. Thus, 28.26% products were out of IP specification products and 13.04% products were considered as substandard products.

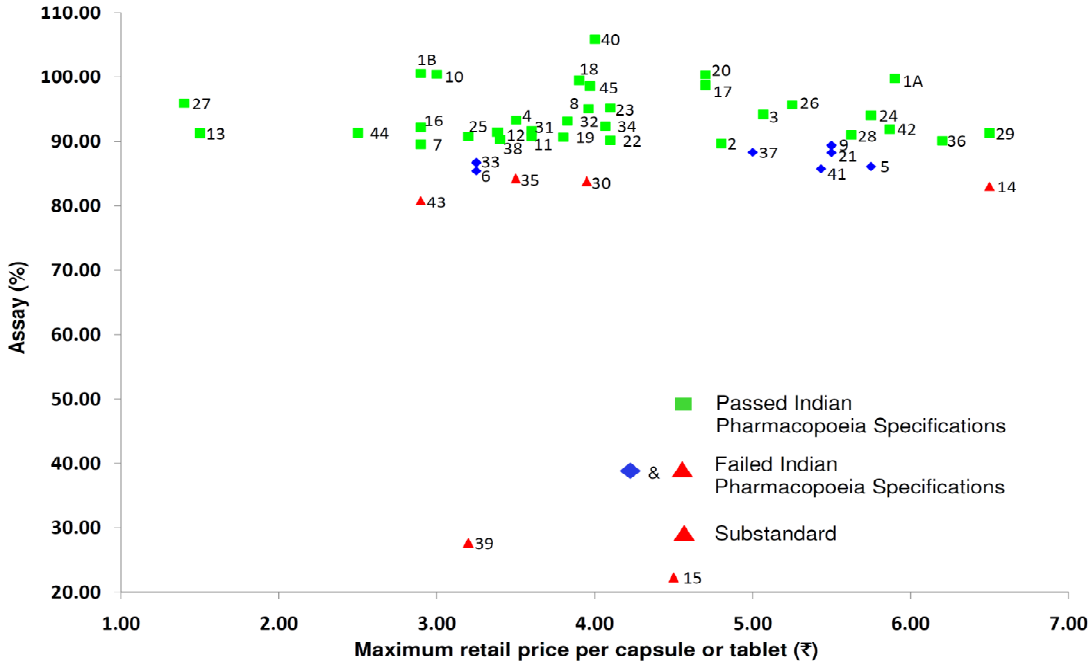

Fig. 1 Maximum retail price versus mean assay plot showing amoxicillin generic products (N=46) quality

Fisher's exact test with two tailed p-value 0.87 showed no significant difference between assay and price of the evaluated products. It can be concluded that several products available in the market are of substandard quality. High extremity of this situation that is quality is not significantly related to low cost only as shown in Table 1.

Table 1 Price wise distribution of passed and failed AMOX products

Maximum retail price per capsule/tablet (₹)	No. of products failed	No. of products passed
1-2	-	2
>2-3	1	5
>3-4	6	11
>4-5	2	5
>5-6	4	6
>6-7	1	2

Results for diclofenac sodium

According to the recommended ICH guidelines Q2 (R1) proposed method was validated. Out of total 32, 34.37% of products failed to pass the pharmacopoeia specification and 15.62% lied under 'Category B' for substandard quality mentioned by CDSCO, New Delhi. As shown in Fig. 2, products tagged with high price do not guarantee the good quality and product of low price do not ensure poor quality. After demonstrating Fisher's exact test, a two tailed p-value 0.43 showed no significant difference between price and assay value. It indicates poor quality products exist in the market irrespective of the price and these substandard products range from low price to high price. High severity of underlying situation, as indicated by the results was not significantly related to low cost only as show in Table 2.

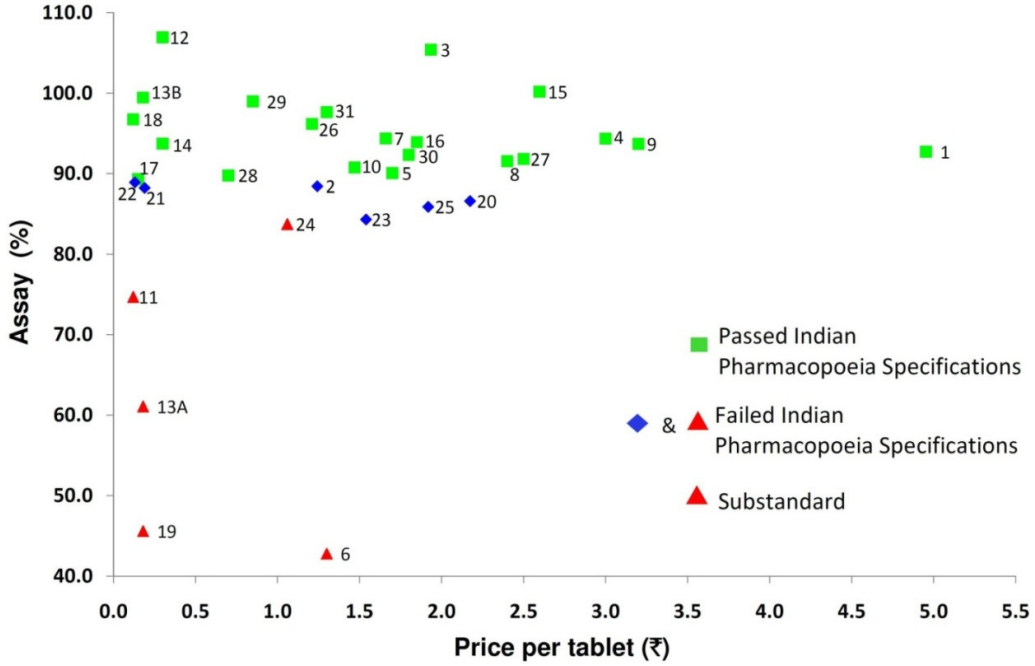

Fig. 2 Maximum retail price versus mean assay plot showing diclofenac generic products (N=32) quality

Table 2 Price wise distribution of passed and failed DICLO products

Maximum retail price per tablet (₹)	No. of products failed	No. of products passed
0.1-0.5	5	5
>0.5-1	-	2
>1-2	5	8
>2-3	1	3
>3-4	-	2
>4-5	-	1

Objective 2

To develop and validate identification and quantitative models using near infrared spectroscopy and chemometric analysis for :
(a) amoxicillin trihydrate capsule; and
(b) diclofenac sodium tablet

Expanding market of pharmaceuticals demands the fast and efficient process to evaluate their quality. Seven national testing laboratories of India have the average annual capacity of 15000 samples for evaluation by using conventional techniques like UV spectroscopy and HPLC. Moreover, many private testing laboratories also work for the regulatory authorities to explore the quality. However, these conventional techniques do not attain the complete demand due to time consuming and expensive nature. Therefore, methods like near infrared spectroscopy has promising feature for testing the quality of pharmaceuticals in a very fast and efficient manner.

Instrument and software

A Thermo Scientific Antaris II FT-NIR analyzer equipped with an integrating sphere coupled with indium gallium arsenide (InGaAs) detector was employed to generate diffuse reflectance spectra and data was collected by means of inbuilt RESULT software. A HPLC (Waters, Milford, MA, USA) equipped with Alliance 2695 separations module and 2996 photodiode array detector was used in reference analysis using octadecylsilane bonded C-18 (250mm×4.6mm,5µm) column. All samples during analysis were weighed using TB-215D (Denver Instrument, Germany) analytical balance. All chemometric data analysis and modeling were carried out using chemometric software package TQ Analyst 7.2.0 (Thermo Fisher Scientific Inc., MA, USA), along with the R version 3.0.3 and statistical software MATLAB version 7.6.0 (MathWorks, Natick, USA).

A. Model development and validation for amoxicillin trihydrate capsule

Many researchers have been worked on NIR-chemometric models for qualification and quantitation of amoxicillin [43], [44]. However qualitative identification model which can identify AMOX in capsule from other similar molecules like ampicillin and cefadroxil; and quantitatively analysis of same API in capsule formulations which are analogous to commercial product has not been reported previously. Therefore using our developed spectral library we designed models based on diffuse reflectance that can be used for AMOX identification and quantitation in capsule formulations; and these capsule were very similar to commercial products. Adding new spectra of new amoxicillin product or batch will update calibration model which will facilitate easy and direct comparison between different products without the use of reference samples in future.

Method

Preliminary study

Latent variables (LV) and number of optimal scan were estimated after conducting preliminary analysis and as a result 6 latent variables for maximum variability and 32 scans were found adequate for superior precision. In accordance with American Society for Testing and Materials (*ASTM*) guidelines; ample number of training or calibration samples that is 6 × (number of LVs + 1) and test or validation samples that is 4 × (number of LVs) are recommended for making model [44]. Thus 78 compositions in total were formulated and divided in to calibration (training) and validation(test) set according to ASTM guidelines.

Capsule content formulation and NIR data acquisition

Each capsule formulation was comprised of amoxicillin trihydrate equivalent to 250 mg of amoxicillin. It was used as an active pharmaceutical ingredient in a range of approximately 50-110% of 250 mg amoxicillin. AMOX and added excipients at different quantity were formulated by quadratic mixture modeling [45] and blended. There 78 compositions were prepared in total. Model was developed with a set of 50 calibration standards known as training set and validated with 28 validation standards known as test set containing the same original AMOX range as in calibration samples. A placebo of excipients (microcrystalline cellulose, croscarmellose sodium, magnesium stearate and colloidal silicon dioxide) in equal amount was also formulated and the total content of each formulation was divided into three aliquots. Simultaneously spectra were recorded in triplicate using integrating sphere in diffuse reflectance mode at 8 cm^{-1} resolution over the spectral range of 4000–10,000cm^{-1}. Hence 711 spectra were procured totally on account of 78 formulations including placebo.

Reference method

Indian Pharmacopoeia prescribes IR and HPLC for identification and assay respectively for amoxicillin trihydrate product[16]. Thus being highly sensitive; HPLC was preferred for both identification and assay. Resulted assay values were used as reference values in NIR-chemometric model development.

Model development and validation

Validation samples must be independent and cannot be included in training set during development. Therefore, samples used as independent validation set were divided in to two sets; internal validation set or test set and external validation set.

Identification

On the ground of mahalanobis distance, kennard-stone algorithm [46] was used for selecting 50 calibration standards out of 78 formulations using prospectr package in R software [47]. During optimization, three outliers were observed and model was optimized after removing two outliers except placebo, as it was included by choice to make the model more accurate. In validation, test set was comprised of 28 samples. And since ampicillin classifies as penicillin; and cefadroxil belongs to cephalosporin family which is much similar to penicillin classin structure. Therefore, external validation set included commercial product of each ampicillin and cefadroxil along with three amoxicillin commercial products. In addition, for the specificity of the model cefadroxil RS was included in external validation set as the negative control to design a robust model. For identification model development three more samples of placebo were added in the calibration set and three were added in validation set.

Using the discriminant analysis algorithm mean spectrums of three aliquots for each sample in triplicate were calculated and distribution model generated by estimating the variance at each data point of spectrum in the range of analysis. Identification model was optimized on training set of 48 samples. With principal component (PC) 6, data described 99.8% variability. Specificity of the model was evaluated with cefadroxil RS as a negative control. Result suggests that the proposed model was well efficient to differentiate amoxicillin from cefadroxil as depicted in Fig. 3.

Quantitative analysis

Using different chemometric pretreatment, 96 models were designed and based on the p-value of intercept and slope along with minimum root mean square error of calibration (RMSEC) and root mean square error of prediction (RMSEP), some models were filtered out. Ultimately a partial least square (PLS) model was finally opted among the filtered models based on suitable latent variable and root mean square error of cross validation (RMSECV) value. Therefore method

in this case used a PLS algorithm with standard normal variate (SNV) as scattering correction. There were 28 samples used as internal validation sample. In accordance with the recommendation of the European Medicine Agency (EMA/EMEA) and ICH validation guidelines[42], [48]; validation were covered using five independent formulations and three commercial real capsules as external validation set.

Like in identification model two outliers were have high leverage thus removed from the calibration set. Therefore quantitative model was also optimized on training set 48 samples using PLS with latent variable up to four which shows maximum spectral information. As a result, good correlation coefficient was found to be 0.9937 with RMSEC 2.17%. The accepted PLS models was eventually used to predict the amoxicillin in test set 28 samples. The accuracy of the NIRS predictive equation was then evaluated using linear regression analysis between NIRS-predicted values and those acquired by the reference HPLC method. Therefore, RMSEP and RMSECV were found to be of 2.38% and 2.43% respectively with four factors or latent variables.

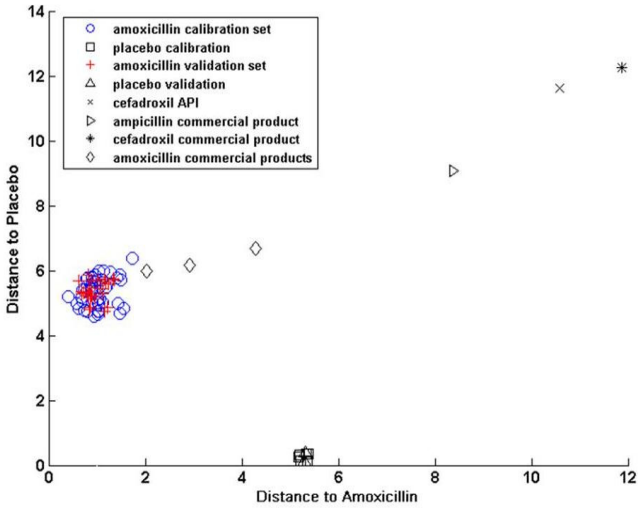

Fig. 3 Identification of amoxicillin sample with respect to distance to amoxicillin based on discriminant analysis algorithm

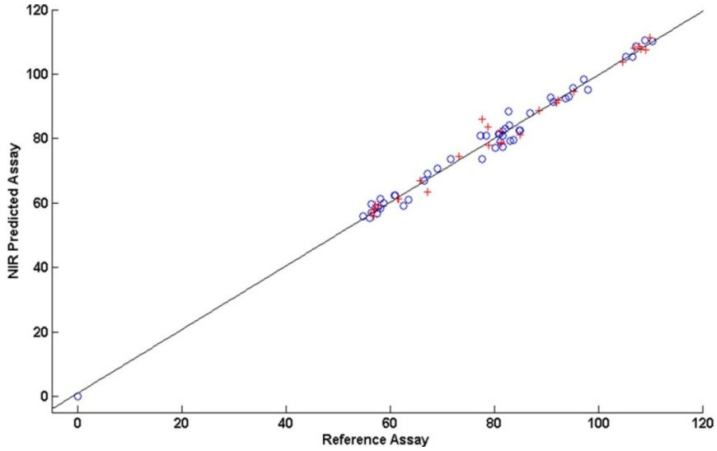

Fig. 4 Linearity plot for amoxicillin calibration (○) and validation (+) samples, solid line shows the data fit

Using external validation set; proposed quantitative model was validated using parameters as recommended like accuracy, precision, linearity and robustness as shown in Table 3 and 4 in accordance with International Conference on Harmonization (ICH) and EMA guidelines. Predicted result from proposed model showed linearity with the reference values as shown in Fig. 4.

Table 3 Accuracy evaluation between proposed and reference method

Sample	Pharmacopoeial HPLC Assay (%)[a]	NIR Predicted Assay (%)[a]	t-test paired p-value
Low	69.75±1.04	67.38±0.57	0.2843
Medium	89.36±0.25	89.92±1.48	0.0994
High	110.01±0.74	109.14±0.14	0.0918

[a]Mean values and standard deviation of each sample in triplicate.

Table 4 Validation parameters for evaluating the proposed NIR model

Validation Parameter	Validation Unit	Value
Accuracy	RMSEC	2.17%
(Figure of merit)	RMSEP	2.38%
	RMSECV	2.43%
Precision	RSD Ist determination	0.65%
(Repeatability)	RSD IInd determination	0.44%
	RSD IIIrd determination	1.37%
Linearity	Slope	0.958
	Intercept	4.580
	Correlation coefficient (*r*)	0.996
Robustness	Predicted AMOX amount at	
	T= 22 ^{o}C	100.2±0.75%(RSD=0.75)
	T= 25 ^{o}C	100.9±1.65%(RSD=1.65)
	T= 28 ^{o}C	100.1±1.22%(RSD=1.22)
	Variation between groups	0.64
	p-value	

Identification and qualitative model assessment

NIR proposed identification and quantitative models were applied on three commercial products and obtained results were finally compared with the result estimated by the reference HPLC method. For identification based on discriminant analysis; all three AMOX commercial sample found close distance to amoxicillin formulated samples while others similar molecules cefadroxil and ampicillin commercial products were clearly distinguished as shown in Fig. 3. In quantitative analysis in order to estimate the content assay from proposed model and reference method; results were compared by applying paired t-test which showed NIR model to be an alternative and effective procedure as reference method as mentioned in Table 5.

Table 5 Amoxicillin market products evaluation by NIR proposed method

Market Sample	Average content weight of 20 capsules (mg)	Product label claim (mg)	Pharmacopoeial HPLC Assay (%)	NIR Predicted Assay (%)	t-test paired p-value
AMOX-01	293.65	250	90.36±0.37	90.29±0.56	0.4554
AMOX-02	294.86	250	93.57±0.5	93.28±1.77	0.6472
AMOX-03	291.76	250	94.65±0.65	96.37±1.65	0.1154

B. Model development and validation for diclofenac sodium tablet

There are only few published reports on evaluation of DICLO API in formulation[49], [50]; in which artificial neural network[49] or transmission mode[50] were used. Therefore, the purpose of this study was to design a quick and accurate model based on diffuse reflectance; to identify and quantify diclofenac from a complex matrix by applying chemometric and NIR spectroscopy.

Method

Preliminary study

After conducting preliminary analysis at 5 latent variables; some trial formulations showed maximum variability and 32 scans were found adequate for superior precision. In accordance with ASTM guidelines ample number of training or calibration samples that is 6 × (number of LVs + 1) and test or validation samples that is 4 × (number of LVs) are recommended for making model [44] Thus 67 compositions were formulated in total and divided in to calibration(training) and validation(test) set according to ASTM guidelines.

Tablet content formulation and NIR data acquisition

Tablet formulation was accomplished using diclofenac sodium as API within a range 70-130% of 50 mg. Often used excipients like microcrystalline cellulose, magnesium stearate, talc, croscarmellose sodium and colloidal silicon dioxide [51], were weighed in range according to specified monographs[52] and blended with DICLO API. Each formulation was divided in to three aliquots and kept in a quartz flat bottom vial. Using Integrating sphere, powder formulation were placed in these vial and diffuse reflectance was measured with in a spectral range of 4000 to 10000 cm^{-1} with 8 cm^{-1} spectral resolution. Equal amount of all excipient were mixed and used as placebo. For each sample, a mean spectrum of triplicate spectrum was used for calculation and each spectrum was collected from the average of 32 scans

Selection of training and test set

Based on the mahalanobis distance, 47 samples (46 formulations and one placebo) and 20 samples were selected as calibration and validation set respectively using Kennard-stone algorithm [46] in 'prospectr' package R software [47]. One placebo sample was intentionally included in the calibration set to make the model more specific and more accurate. For identification model development three more samples of placebo were added in the calibration set and two were added in validation set. Five formulations which were independent to the training or test set were also prepared as external validation set for qualitative model validation.

Reference method

Identification and quantification of all samples were processed using in house validated HPLC method against diclofenac sodium RS. Peak purity was evaluated with lower purity angle then purity threshold. HPLC assay results were used as reference for the chemometric modeling.

Model development and validation

Identification method development and validation

Discriminant algorithm was used to develop identification model. Full NIR spectral range was found to be rich in information. Six samples were removed as outlier from the calibration set due to more distance from the diclofenac method model. With PC 5 data showed the 99.2 % variability. Specificity of the model was analyzed using an aceclofenac tablet market product as negative control and five commercial diclofenac sodium tablets of 50 mg label claim and the resulted data signified the developed model as a well compatible model to identify DICLO as shown in Fig. 5.

Quantitative method development and validation

Using different chemometric pretreatment, 96 models were designed and based on the p-value of intercept and slope along with minimum root mean square error of calibration (RMSEC) and root mean square error of prediction (RMSEP), some models were filtered out. And finally a PLS model was opted based on suitable latent variable and RMSECV result. The correlation between the spectra and reference values was examined using this established PLS model, and was optimized by cross-validation. This model was developed with constant pathlength and without any spectral pretreatment that is constant pathlength. Leverages were identified by the Chauvenet test, in which seven samples were found as outliers. Therefore except placebo, six leverages were removed from the calibration set. Subsequently calibration was done and latent variable was found to be 5 to show optimum spectral information. Then calibration set was comprised of 41 samples. Finally a good correlation coefficient was established to be 0.999 with RMSEC 1.52 mg and RMSEP 1.66 mg. Linear regression analysis between predicted and reference result were accomplished, which signified high degree of correlation r=0.9919 as shown in Fig. 6. In order to confirm the result with respect to data exemption by over fitting; RMSECV was estimated. Thus; at factor five' model showed least RMSECV which was 2.34 mg.

Using external validation set; proposed quantitative model was validated using parameters as recommended by ICH and EMA guidelines like accuracy, precision, linearity and robustness as shown in Table 6 and 7. Predicted result from proposed model showed linearity with the reference values as shown in Fig. 6.

Model assessment on commercial DICLO products

NIR-chemometric proposed method was demonstrated using five commercially available diclofenac sodium products. For identification an aceclofenac market product and five diclofenac market products were tested. As shown in Fig. 5. aceclofenac showed more distance than diclofenac formulations. Four diclofenac products were near the proximity of formulated samples while a product that is DICLO-3 was far away. Thus, for passing the identification test a value of 4.5 as distance from diclofenac was fixed as threshold. For quantitative assessment 20 tablets of each product were crushed in mortar and pestle and coated particles were removed through sieving. Tablet powder was analyzed in triplicate. As shown in Table 8, the result of prediction from proposed model and reference method was obtained. Upon paired t-test, only DICLO-02 and DICLO-04 were accurately quantified by the proposed NIR-chemometric model. Products failing in analysis by the model showed high chemometric uncertainty which may be due to presence of different excipients, different particle size or different source of API, which can be overcome by

adding more API from different sources in the spectral library of the model and recalibrate the model.

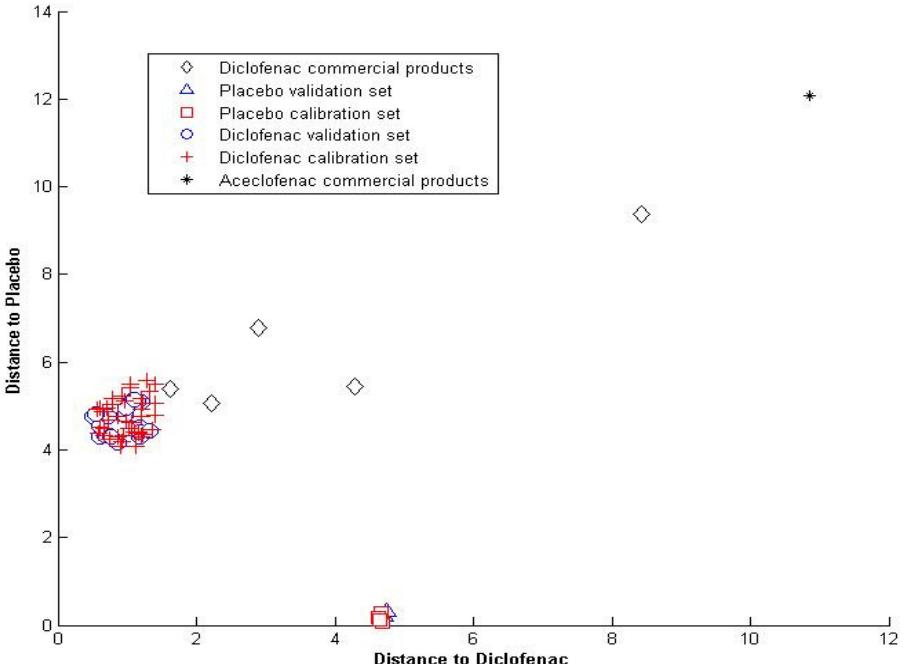

Fig. 5 Identification of diclofenac sample with respect to distance to amoxicillin based on discriminant analysis algorithm

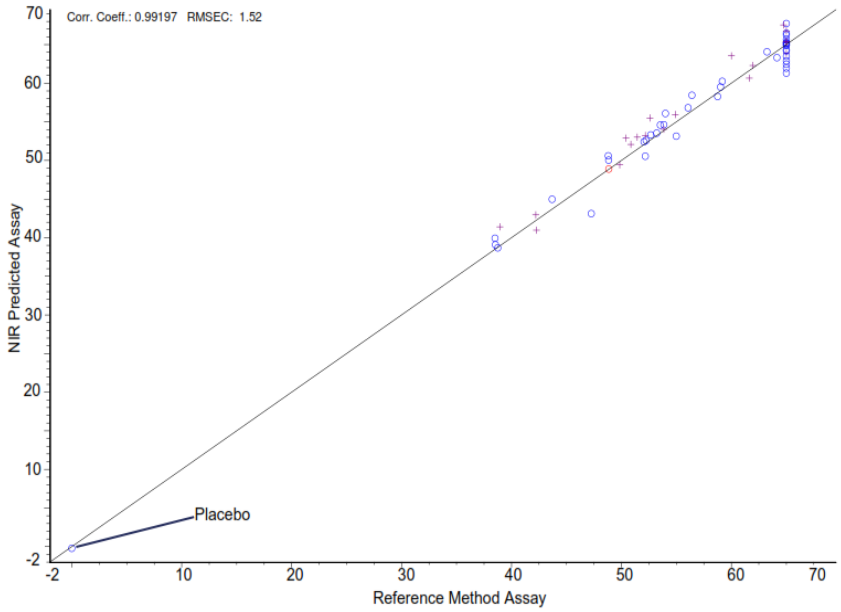

Fig. 6 Linearity plot for diclofenac calibration (○) and validation (+) samples, solid line shows the data fit

Table 6 Accuracy evaluation between proposed and reference method

Sample	Pharmacopoeial HPLC Assay (mg)[a]	NIR Predicted Assay (mg)[a]	t-test Paired p-value
Low (70%)	35.19±0.20	35.46±0.34	0.46
Medium (80%)	39.93±0.07	40.12±0.27	0.24
High (110%)	55.16±0.21	55.30±0.30	0.36

[a]Mean values and standard deviation of each sample in triplicate.

Table 7 Validation parameters for evaluating the proposed NIR model

Validation Parameter	Validation Unit	Value
Accuracy	RMSEC	1.52 mg
(Figure of merit)	RMSEP	1.66 mg
	RMSECV	2.34 mg
Precision (Repeatability)	%RSD Ist day	0.62
	%RSD IInd day	0.71
	%RSD IIIrd day	0.65
Linearity	Slope	1.004
	Intercept	-0.329
	Correlation coefficient (*r*)	0.999
Robustness	Predicted DICLO amount (mg) at	
	T= 22 ^{o}C	49.52±0.60 (%RSD=1.21)
	T= 25 ^{o}C	49.96±0.41 (%RSD=0.81)
	T= 28 ^{o}C	49.55±0.52 (%RSD=1.06)
	Variation between groups	
	p-value	0.35

Table 8 Diclofenac market products evaluation by NIR proposed method

Market Product	Product Label Claim (mg)	In-house HPLC Assay (mg)	NIR Predicted Assay (mg)	t-test Paired p-value
DICLO-01	50	48.80±0.29	37.41±0.15	0.00
DICLO-02	50	47.08±1.35	46.72±0.08	0.63
DICLO-03	50	19.96±0.02	16.39±0.25	0.04
DICLO-04	50	46.11±0.39	46.68±0.19	0.05
DICLO-05	50	43.77±0.28	48.36±0.26	0.03

Objective 3

To conduct two cross sectional surveys:
(a) to demonstrate medicine prescribing preference by medical practitioners and their perspective for medicine therapeutic response and adverse effects with respect to quality of medicines; and additionally to demonstrate the patient compliance;
(b) to demonstrate the prevalence of treatment adherence and compliance by patients; and most imprudent age, gender and monthly income groups of patients with respect to rational use of medicines

Among various challenges to improve the healthcare system medical practitioners (MP) knowledge about medicine has principle concern. Prescribing appropriate and affordable medicines prior to the commencement of treatment ensures the safety and satisfaction of patient specifically poor patients. Like after diagnosis, only medicine play important role in mitigation, cure and prevention of disease or infection. However, an issue emerges from the patient side like with increasing chaotic burden of life, the willingness and regularity of treatment schedules are reduced enormously among patients. This concept of treatment non adherence or treatment noncompliance has led to severe consequences of reduction in clinical benefit and increased risk of morbidity and mortality in the patients[53]. Therefore medical practice considered as the responsibility for overall clinical results so that quality of healthcare may improve in regular practice. On such grounds a cross sectional survey was required to know the views and experience of MP in order to take some actions for improving the public health. Also little consideration has been paid to patients' thoughts regarding medicines, and such thoughts may have significance for working out the non-adherence to medication. It was the survey on patient regularity which covers their adherence and compliance in treatment. Subjective self reports are the extensively used concept which is simple, fast, inexpensive and least resource intensive and highly useful in clinic interview and large scale assessment[54], [55]. Thus a patients' survey questionnaire was designed in order to achieve our purpose. Such survey would help in indentify the most imprudent community sector in terms of age, gender and monthly income group with respect to rational use of medicines.

A. Medical practitioner's survey

Study design and method

The survey instrument was a questionnaire conducted online and face-to-face interview which consisted of several multiple choice questions related to medicine prescribing preference, therapeutic response (TR) and adverse effects (AE) of three standards in market like Innovator Branded Generic (IBG), Branded Generic (BG) and Generic (G) products. Scale used for multiple choice questions were less, moderate and most preferable for prescribing preference; good, moderate, mild and poor for therapeutic response; none, mild, moderate, high and severe for adverse effects (scale degree mentioned in Table 9).

Data Analysis

Descriptive statistics were used to examine the perspective of the MP. The Chi-square test was used to examine the associations between different attributes. Statistical analyses were performed using the SPSS software, version 17.0, and statistical significance was assumed for p-value less than or equal to 0.05.

Result

Out of 111 medical practitioners, 47.7% (including which were not mentioned their specialization) were general physician and 26.1% were dentist. Among all 53.2% MP were having more than ten years of experience as Table 10 shows the sample profile of the survey respondents. In terms of most preferable medicines 21.6%, 63.1% and 19.8% MP prescribe the IBG, BG and G respectively, while as less preferable medicines 28.8%, 4.5%, 41.4% MP prescribe IBG, BG and G respectively as shown in Fig. 7. About 59.5% and 64.9 % MP considered IBG and BG respectively having good TR, while G has good TR according to only 15.3% MP as depicted in Fig. 8.

Chi-square test between prescribing preference and adverse effect of three tested standards shows no association as $p>0.05$ in all cases. However, significant association found between prescribing preference and therapeutic response of BG X^2 (4, N=111) = 21.751, $p<0.05$ and G X^2 (6, N=111) = 19.486, $p<0.05$ but no association in case of IBG X^2 (6, N=111) = 14.068, $p>0.05$.

Table 9 Scale for interactions and adverse effects

Scale for Adverse Effects
None: no adverse effect observed
Mild: require only substitution by new medicine product
Moderate: require high attention and addition of new medicines product and/or substitution by new medicines products
High: require immediate treatment
Severe: require immediate hospitalization

Table 10 Sample profile of medical practitioners, N=111

Demographic Variables		Frequency	Percent
Location			
	Uttar Pradesh	35	31.5
	Uttarakhand	4	3.6
	New Delhi/Delhi	21	18.9
	Haryana	2	1.8
	Punjab	2	1.8
	Himachal Pradesh	27	24.3
	Jammu and Kashmir	20	18.0
Qualification*			
	M.B.B.S.	21	18.9
	M.D.	33	29.7
	M.S.	1	0.9
	B.D.S.	29	26.1
	B.U.M.S.	9	8.1
	B.A.M.S	11	9.9
	Higher Degree (DM, Mch, DNB etc)	4	3.6
	Others: M.D. in Ayurveda/Unani/Dental	3	2.7
Specialization			
	Dentist	29	26.1
	Dermatologist	8	7.2
	Diabetologist	3	2.7
	ENT Specialist	1	0.9
	General Physici	40	36.0
	Gynaccologist	4	3.6
	Neonatologist	1	0.9
	Not Mentioned	13	11.7
	Opthalmologist	1	0.9
	Orthopedic	1	0.9
	Pediatrician	8	7.2
	Preventive Medi	1	0.9
	Radiologist	1	0.9
Practicing Experience			
	Up to 1 Year	8	7.2
	Up to 2 Year	20	18.0
	Up to 4 Year	7	6.3
	Up to 6 Year	4	3.6
	Up to 8 Year	10	9.0
	Up to 10 Year	2	1.8
	More than 10 Year	59	53.2

Perspective on AE, 69.4%, 65.8% and 55% MP considered IBG, BG and G respectively having mild AE; and 2.7%, 0.9% and 8.1% believed IBG, BG and G respectively having high AE as depicted in Fig. 9.

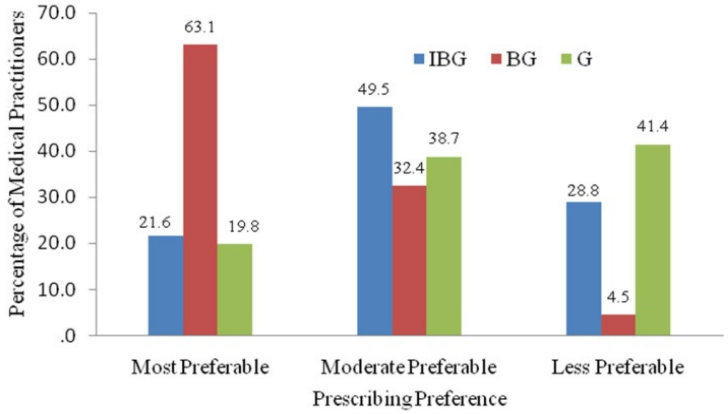

Fig. 7 Prescribing preference of IBG, BG and G medicines by medical practitioners

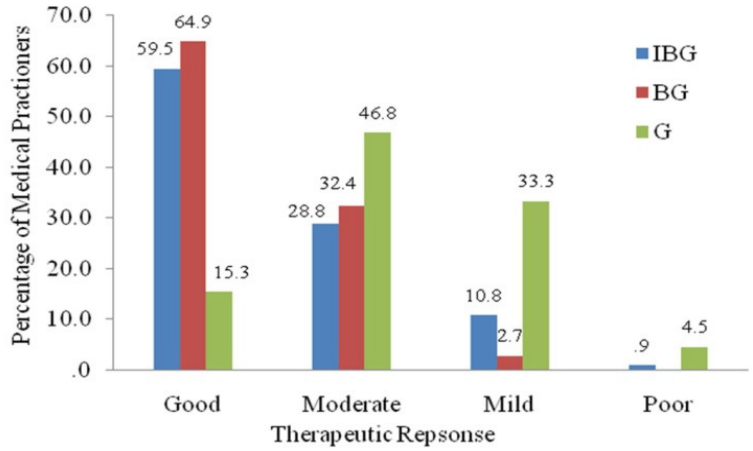

Fig. 8 Therapeutic responses views on IBG, BG and G medicines by medical practitioners

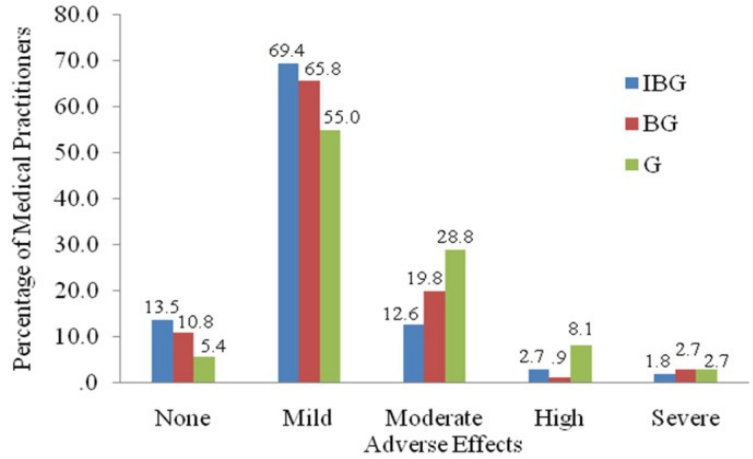

Fig. 9 Adverse effects views on IBG, BG and G medicines by medical practitioners

For determining the patient adherence or compliance to MP's instruction, result showed that only one MP said that all his patients follow his 100% instructions; whereas 33.3%, 51%, 18% said their all patients follow their 70-90%, 40-60% and 10-30% instructions respectively, while 3.6% said their all patient do not follow any instruction as shown in Fig. 10.

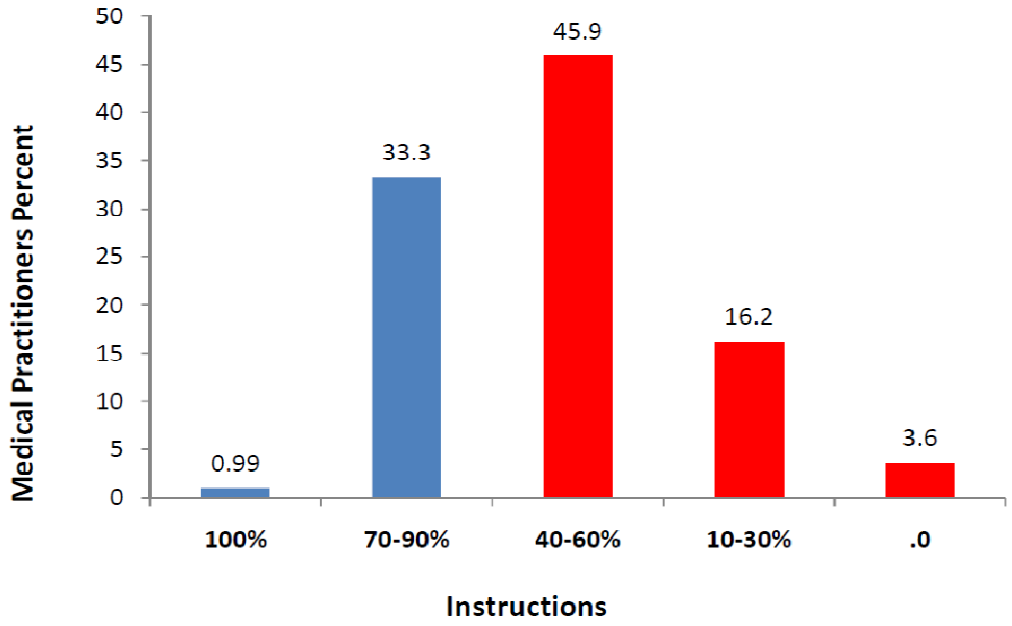

Fig. 10 Medical Practitioner (N=111) perspective on compliance by their all patient

B. Patients' survey

Study Design

A one way out to assess the adherence encompasses direct behavior observation or therapy surveillance. Questionnaires which relate to specific medical tendency to determine specific behavior may be the preferable predictors for measuring the adherence. Thus to obtain subject perspectives, we conducted cross sectional survey; based on self reported questionnaire by a large population from six north Indian states and one Union territories; which were Uttar Pradesh, Uttarakhand, Haryana, Himachal Pradesh, Punjab (including Chandigarh), Jammu & Kashmir and Delhi. We attempted to collect data via face-to-face interviews of 4161 patients near hospital areas, residential locations, colleges and schools or to be filled by their guardians in case of minor age group. Therefore this research demonstrate the variation in medication adherence tendency of the respondents who were patient or were be a sufferer in past. This survey was conducted between June 2014 and August 2015.

Method

We created two measures of adherence, first was how many patients stop medication before completion of treatment when getting relief; and second was how many patients miss doses during treatment. We also measured compliance towards the medical practitioner's instructions. For these measures, we identified most imprudent community groups; like age, gender and monthly income of family with their non adherence and non compliance practice.

For analysis the survey data statistical analyses were performed using the SPSS software, version 17.0, and statistical significance was assumed for p-value less than or equal to 0.05. For

determining the association between different variable Chi-square tests on contingency tables was applied.

Table 11 Sample profile of patients, N= 4161

Demographic variables		Frequency	Percent
Age (years)			
	Below 19	1008	24.2
	20-24	796	19.1
	25-34	822	19.8
	35-44	694	16.7
	45-54	546	13.1
	55-64	218	5.2
	Above 65	76	1.8
Gender			
	Male	2563	61.6
	Female	1597	38.4
Location			
	Delhi	555	13.3
	Himachal Pradesh	700	16.8
	Haryana	556	13.4
	Jammu & Kashmir	451	10.8
	Punjab	215	5.2
	Uttar Pradesh	889	21.4
	Uttarakhand	795	19.1
Monthly Income (₹)			
	2000-5000	890	21.4
	5001-10000	1062	25.5
	10001-20000	968	23.3
	20001-30000	601	14.4
	More than 30000	638	15.3

Result

As shown in Table 11, 4161 respondents were from teenagers to more than 65 years of age; and they were further classified based on monthly income and gender. Respondents were randomly selected from all over Northern India. Patient tendency towards compliance or following the instructions of medical practitioners during the treatment showed that only 26.2 % patients show full compliance and about 73.8 % show non compliance. Even more than 20% patients follow half or less than half of the instructions as shown in Fig. 11. It indicates that these patients are at high risk. As shown in Fig. 12. patient tendency to stop medication before completion of treatment showed that 44.1% of the patients do not adhere to the treatment, which means that when these respondents get some relief, they follow a tendency to stop medication before one or two day and sometimes in mid of the treatment without asking medical practitioners. Moreover 53.8% of respondents generally miss one, two, three and even four or more doses during treatment as shown in Fig. 13.

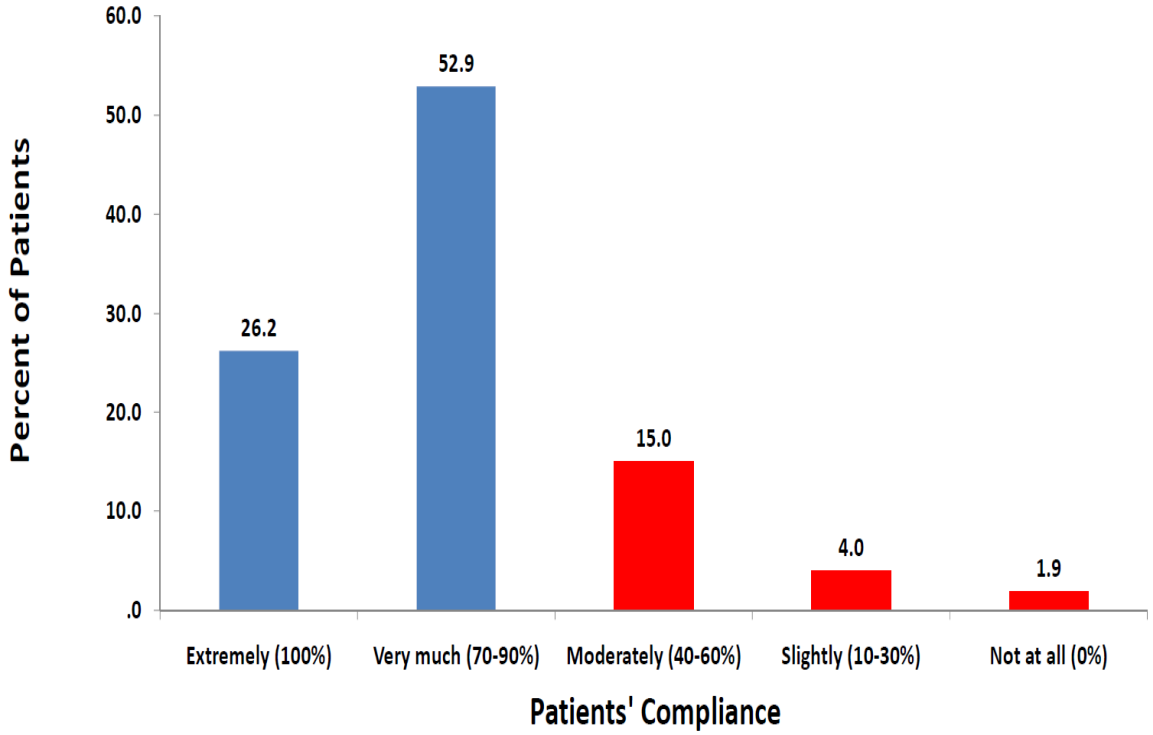

Fig. 11 Compliance of Patient (N=4161) in respect to following the instructions of medical practitioners

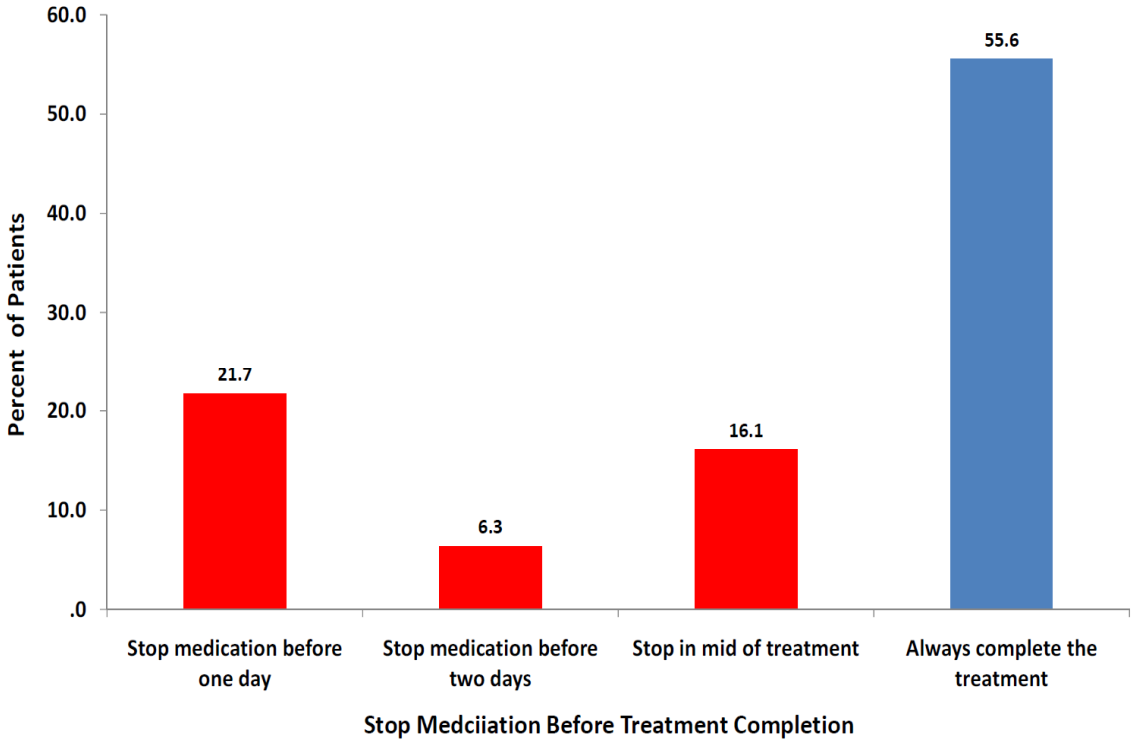

Fig. 12 Stop medication tendency of patients (N=4151) before completion of treatment

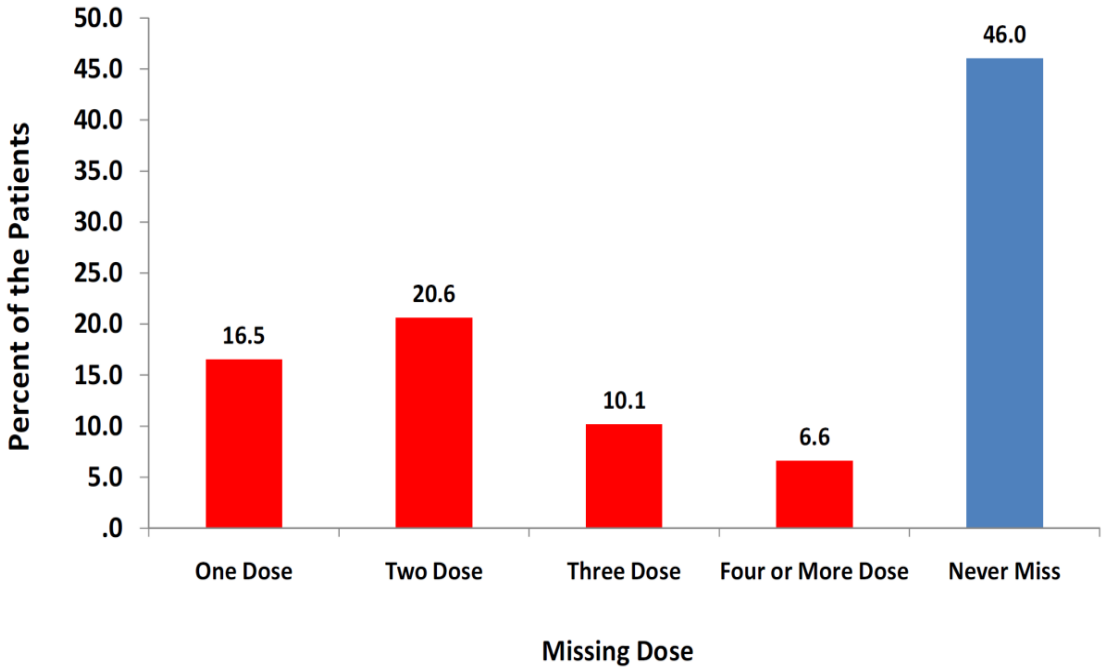

Fig. 13 Missing dose tendency of patients (N=4160) during treatment

Table 12 Chi square test for association between different categorical variables

Behavior	Age	Gender	Monthly Income
Stop Medication Before Treatment Completion	p=0.063 X^2=40.273 df=28 N=4157	p=0.004 X^2=22.343 df=8 N=4157	p=0.0 X^2=166.110 df=16 N=4155
Missing Dose	p=0.002 X^2=54.772 df=28 N=4160	p=0.023 X^2=17.730 df=8 N=4160	p=0.00 X^2=113.888 df=16 N=4158
Compliance	p=0.0 X^2=76.193 df=28 N=4161	p=0.480 χ=7.536 df=8 N=4161	p=0.0 X^2=109.148 df=16 N=4159

Note: p= p-value, X^2= chi square critical value, df= degree of freedom, N= number of patients

To ensure the relationship between different variables, Chi-square test was applied as shown in Table 12. There was no relationship between stop medication before treatment completion and age. Moreover, as demonstrated by Chi square test with a p-value greater than 0.05, more than 53% respondents (N=1005) who were below 19 year of age do not complete the treatment on getting

relief without asking the medical practitioners. Maximum non adherence is shown by the age group between 20-24, and maximum adherence by the group above 65 year of age.

With missing dose tendency and age Chi-square test determined the significant relationship with p-value less than 0.05. In this case, 43.3% respondents (N=76) above 65 age have missing dose behavior. About 56.3% respondents (N=822) between age 25-34 have the tendency to miss the dose and 51.2% respondents (N=1007) below age 19 have the tendency to miss the dose. Thus, except people above 65 ages, with increase in age missing dose behavior also increases.

In the same way Chi-square test with contingency table between compliance and age showed significant relationship with p-value less than 0.05 More than 80% of respondents between 20-24 age (N=796); and more than 77% of respondents below 19 years age (N=1008) do not show compliance.

Women are less irregular then men towards stop medication before treatment completion as shown by the result. Patients' gender was significantly associated with this adherence tendency with a p-value less than 0.05. As there were 24.1% males (N=2560) and 18.1% females (N=1596) stop medication one day before the treatment complete; also 53.5 % males (N=2560) and 59.0% females (N=1596) always complete the treatment as well.

Patients' gender and missing dose tendency has a significant relationship as observed in this study with p-value less than 0.05. About 10.1% males and 6.4% females have the tendency to miss one dose during treatment. About 13.5% males and 7.1% females have the tendency to miss two doses during treatment. About 44.5% males (N=2562) and 48.5% females (N= 1597) never miss the dose. However, instructions following behavior have not significant relationship with gender as determined by p-value greater than 0.05.

On demonstrating the Chi-square test, p-value less than 0.05 shows, patients' adherence behavior has significantly associated with family monthly income. About 34% (N=638) patients who have monthly income more than Rs. 30000 do not complete the treatment. More than 52% (N=1061) patients who have monthly income between Rs. 5001-10000 do not complete the treatment. More than 46% (N=889) patients who have monthly income between Rs. 2000-5000 do not complete the treatment. Except lowest income group, as the family monthly income increase patient adherence to complete the treatment increases.

Similarly, missing dose behavior also has significant relationship with the monthly income shown by p-value less than 0.05. About 54% (N=4158) respondents of all income group have the tendency to miss the doses. Missing dose behavior is estimated within groups shows respondents who have Rs. 5001-10000 monthly income have maximum tendency to miss the dose while the group having more than Rs. 30000 monthly income have minimum missing dose behavior. Second most prone group to miss the dose is group having Rs. 2000-5000 monthly income.

Instructions following tendency has also the significant relationship with monthly income having p-value less than 0.05. Lowest and highest income group have the maximum compliance tendency. More than 78% (N=968) respondents who have Rs. 10001-20000 monthly income, were not shown compliance. More than 77.5% (N=1062) respondents who have Rs. 5001-10000 monthly income do not show compliance.

Conclusion

No study has been performed on the quality of market products in the last few years and the real extent of the poor quality or substandard medicines still remains ambiguous. This study found high prevalence of poor quality of amoxicillin 28.26% (N=46) and diclofenac 34.37% (N=32) generic products in the Indian market. The potential consequence of such under dose medications is a matter of concern to the regulatory authorities. Under urgency it is required to focus on controlling the availability of substandard drugs in the market that are produced as a result of the

poor manufacturing and quality-control practices or deliberately falsified drugs. Worldwide awareness has been growing on the increasing incidence of substandard and spurious drug, whereas India is still lagging on the issue. Thus, to counteract the issue of spurious and substandard quality medicine in India there is an urgent need for additional research or routine analytical evidences to explain the magnitude of the problem across the country.

Evaluation with the conventional methods is time and money consuming. Evaluation of large number of samples of amoxicillin and diclofenac formulations can be sorted out by using the developed identification and quantification near infrared -chemometric models. Therefore, for reliability and time saving features; NIR-Chemometric procedures were intended to be an alternative for the existing analytical techniques.

Generic medicines are highly recommended by the regulatory bodies, however due to poor therapeutic response; most of medical practitioners do not prefer generic medicines. It indicates some quality gaps exist and therefore a medicine monitoring event program must be conducted by the regulatory bodies. Another challenge is how consumption of medicines by patients should be monitored to address the underlying result of non adherence and non compliance. About 73.9% (N=4161) patient do not show full compliance as they reported, while as per 99.1% medical practitioners; their all patient do not show full compliance.

Strategies to monitor and improve adherence are key components of pharmaceutical care plans, especially for patients with chronic diseases, such as hypertension, diabetes, and atherosclerotic heart disease. One of the primary steps in estimating non adherence is to identify which patients are at high risk of this problem. Therefore this study addressed the prevalence of non adherence and compliance across the Northern India. This study showed that 44.1% (N=4151) of the patients stop medication during treatment before its completion and 53.8% (N=4160) of patient generally miss one or more than four doses in between treatment which show high prevalence of non adherence to the treatment. Patients who had Rs. 5001-10000 monthly income have more tendency to miss the dose while the group having more than Rs. 30000 monthly income have minimum missing dose behavior. About 80% (N=796) patients between 25-34 years age and 77% (N=1008) below 19 years of age are more imprudent in showing non compliance. Women are somewhat more regular in showing adherence as when get relief during treatment; 18.1% females (N=1596) and 24.1% males (N=2560) stop medication one day before the treatment complete. The complexity of elements that correspond to non-adherence cannot be trivialized but this research tend the regulatory authorities to design interventions for the most affected segment of the community and help policy maker to plan some efficient program to solve this problem for the best use of medicines.

This exploring research demonstrates that regulatory authorities have to look into these issues for the ways to improve the situation and empower the patients. Therefore, they must confront them as new challenges with respect to patient safety; which ultimately may improve healthcare system, reduce financial burden on patients and enhance the trust on healthcare system.

Research Papers

[1] **A. N. Khan** and R. K. Khar, "Current scenario of spurious and substandard medicines in India: A systematic review," *Indian Journal of Pharmaceutical Sciences*, vol. 77, no. 1, pp. 2–7, 2015.

[2] **A. N. Khan,** A. Kaur, R. K. Khar, and S. Khanam, "Medicine prescribing preference and patient adherence: perspectives of Indian medical practitioners," *Journal of Young Pharmacist*, vol. 8, no. 1, pp. 1–9, 2016.

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Appendices

A. Survey questionnaire for medical practitioners

1. Filling Date: (DD/MM/2014)

***2. Your current location:**

- ◯ Uttar Pradesh
- ◯ Uttarakhand
- ◯ New Delhi/Delhi
- ◯ Haryana
- ◯ Punjab
- ◯ Himachal Pradesh
- ◯ Jammu & Kashmir
- ◯ Others

***3. Your Qualification: (You can select more than one option)**

- ☐ M.B.B.S.
- ☐ M.D.
- ☐ M.S.
- ☐ B.D.S.
- ☐ B.U.M.S.
- ☐ B.A.M.S.
- ☐ Higher Degree(DM, Mch, DNB etc.)
- ☐ Others: M.D in Ayurveda/Unani/Dental

***4. Your professional specialization?**
(Note: Like General Physician, Cardiologist, Gynecologist, Neurologist, Orthopedic, Pediatric etc)

5. Your practicing experience in medical profession?

- ◯ Up to 1 Year
- ◯ Up to 2 Years
- ◯ Up to 4 Years
- ◯ Up to 6 Years
- ◯ Up to 8 Years
- ◯ Up to 10 years
- ◯ More than 10 Years

＊6. Which medicine products you preferentially prescribe?
(Note:
#Innovator Branded Generic : Generic products of those companies who are highly involved in inventions, research and manufacturing

#Branded Generic : Generic products of those companies who are highly involved in research and manufacturing

#Generic: Generic products of those companies who are involved in only manufacturing)

	Less Preferable	Moderate Preferable	Most Preferable
Innovator Branded Generic Products (for eg. products of Eli Lilly, Pfizer, GSK, Novartis etc.)	◯	◯	◯
Branded Generic Products (for eg. products of Ranbaxy, Dr. Reddy's, Zydus Cadila, Cipla etc.)	◯	◯	◯
Generic Products (for eg. products of ZenLabs, Alto Healthcare, Ind-swift etc.)	◯	◯	◯

＊7. What are your general views about therapeutic response of:
(Note--
 # Poor : Ineffective & Patient Always Complain

 # Mild : Less Effective & More Complains

 # Moderate : Effective & Few Complains

 # Good : Always Effective & No complain)

	Poor	Mild	Moderate	Good
Innovator Branded Generic Products	◯	◯	◯	◯
Branded Generic Products	◯	◯	◯	◯
Generic Products	◯	◯	◯	◯

***8. What are your general views about price of :**
(Note:
 # No Idea- No Idea about price

 # Non Affordable- For the person whose per day living cost is less than $2.0

 # Moderate- For the person whose per day living cost is less than $2.0

 # Affordable - For the person whose per day living cost is less than $2.0)

	No Idea	Non Affordable	Moderate	Affordable
Innovator Branded Generic Products	◯	◯	◯	◯
Branded Generic Products	◯	◯	◯	◯
Generic Products	◯	◯	◯	◯

***9. What are your general views about adverse effects of :**
(Note :
 # None- No adverse effects observed

 # Mild: Require only substitution by new medicines products

 # Moderate: Require high attention and addition of new medicines products and/or substitution by new medicines products

 # High: Require immediate treatment

 # Severe: Require immediate hospitalization)

	None	Mild	Moderate	High	Severe
Innovator Branded Generic Products	◯	◯	◯	◯	◯
Branded Generic Products	◯	◯	◯	◯	◯
Generic Products	◯	◯	◯	◯	◯

10. From where you get information about medicine uses?
(Note : Rating Scale :
0-No information from this source
1- Minor,
2-Less,
3-Moderate
4-High,
5-Major)

	0	1	2	3	4	5
Medical Council of India	☐	☐	☐	☐	☐	☐
Medical Representative of Pharmaceutical Companies	☐	☐	☐	☐	☐	☐
Conferences, Workshops, Seminars of Pharmaceutical Companies	☐	☐	☐	☐	☐	☐
Conferences, Workshops, Seminars of Medical or Paramedical Professional Organisations	☐	☐	☐	☐	☐	☐
Self study and knowledge	☐	☐	☐	☐	☐	☐

11. How would you rate your knowledge of Drug-Drug Interactions of those drugs which you prescribed?

◯ **Minimal: aware of few side effects/adverse effects/interactions only as informed by the patient themselves**

◯ **Below average: aware of at least two moderate interactions of each among all the prescribed drugs**

◯ **Average: aware of at least five moderate interactions of each among all the prescribed drugs**

◯ **Good: aware of all moderate and major interactions which are life threatening or require hospitalization but not addition of drugs in the prescription, or substitution of prescribed drug**

◯ **Excellent: aware of all moderate and major interaction which are life threatening or require hospitalization or addition of drugs in the prescription, or substitution of prescribed drug**

12. How would you rate your knowledge of Drug-Food Interactions of those drugs which you prescribed?

◯ **Minimal: aware of few side effects/adverse effects/interactions only as informed by the patient themselves**

◯ **Below average: aware of at least two moderate interactions of each among all the prescribed drugs**

◯ **Average: aware of at least five moderate interactions of each among all the prescribed drugs**

◯ **Good: aware of all moderate and major interactions which are life threatening or require hospitalization but not addition of drugs in the prescription, or substitution of prescribed drug**

◯ **Excellent: aware of all moderate and major interaction which are life threatening or require hospitalization or addition of drugs in the prescription, or substitution of prescribed drug**

13. How many new patients consult you everyday?

◯ **1-20**

◯ **21-40**

◯ **41-60**

◯ **61-80**

◯ **81-100**

◯ **More than 100**

14. How much your instructions followed by how many patients?

	100% Instructions Followed By	70-90% Instructions Followed By	40-60% Instructions Followed By	10-30% Instructions Followed By	0% Instruction Followed By
100% Patients	◯	◯	◯	◯	◯
70-90% Patients	◯	◯	◯	◯	◯
40-60% Patients	◯	◯	◯	◯	◯
10-30% Patients	◯	◯	◯	◯	◯
0% Patient	◯	◯	◯	◯	◯

B. Survey questionnaire for patient

Survey

For Patient/Patient's Guardian

Objective: To know about the patient awareness and experience about medicine, and their participation in healthcare.

Note 1: This survey is being conducted by Dept. of Pharmacy, Jaypee University, Waknaghat, Solan with the permission of Institute Review Board (IRB) , JUIT, Waknaghat, Solan, H.P. India.

Note 2: *All information given by you will be just for academic research only and your personal information will be kept confidential.*

Name :……**Age:**…..…**Gender:** Male/Female , Address(if possible)……..

……Mobile No. (if possible)…….

Your Location(must):_____(Village/Town/City) Date: ___/___/2014

Q.1. What is your family monthly income?

Rs. 2000- 5,000 ☐ Rs.5001-10,000 ☐ Rs. 10,001-20,000 ☐ Rs. 20,001-30,000 ☐ More than 30,000 ☐

Q.2. Which medicine system do you follow?

Allopathic ☐ Unani/ Ayurvedic ☐ Mark **1**—most preferable,
Homeopathic ☐ **2**—preferable,
3—less preferable.

Q.3. Do you get free essential medicines from government hospital under Central or State government scheme?

Not aware about free medicines ☐
Aware and also avail ☐
Aware but do not take ☐

If you are aware but do not take medicine, specify why?..

Because they do not work well ☐ Only few available, not all ☐
Always all unavailable ☐ It takes much time to get ☐

Q.4. If you buy same medicine from two different location and one is you nearby store (your location), what have you observed?

Same response Observed ☐ Near by store medicine have better response than other area store medicine ☐
Nothing Observed ☐ Other area store medicine have better response than my nearby store medicine ☐

Q.5. How much far your medicines are accessible to you?

Up to 2 km ☐ Up to 5 km ☐
Up to 10 km ☐ Up to 20 km or more ☐

Q.6. When you get ill, what you prefer?

Consult to Government Doctor ☐ Mark **1**—most preferable,
Consult to Private Doctor ☐ **2**—preferable,
Consult medical store ☐ **3**—neutral,
Self medication ☐ **4**—less preferable.

Q.7. Do you check on label?

Expiry Date Yes ☐ No ☐ Maximum Retail Price Yes ☐ No ☐

Q.8. In a 5 days treatment, on improvement, what do you do generally? (Without asking doctor)

Stop medication before One day ☐ Stop medication before Two day ☐
Stop in mid of treatment ☐ Always complete the treatment ☐

Q.9. How many times you generally miss medicine dose in between your treatment of 5 days (among 10 doses)?

One dose ☐ Two dose ☐
Three dose ☐ Four or more ☐
Never miss ☐

Q.10. How much percent of instruction do you follow given by your doctor about medicines?

100% ☐ 70- 90% ☐
40-60% ☐ 10-30% ☐
0% ☐

Q.11. Do you save your all (old & new) prescriptions written by your doctor?

100% ☐ 70- 90% ☐
40-60% ☐ 10-30 % ☐
0% ☐